Poverty is the ultimate form of pollution in a world out of balance with people's needs and its own future.

Bella Abzug
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Forum

Fear of Phenolphthalein?

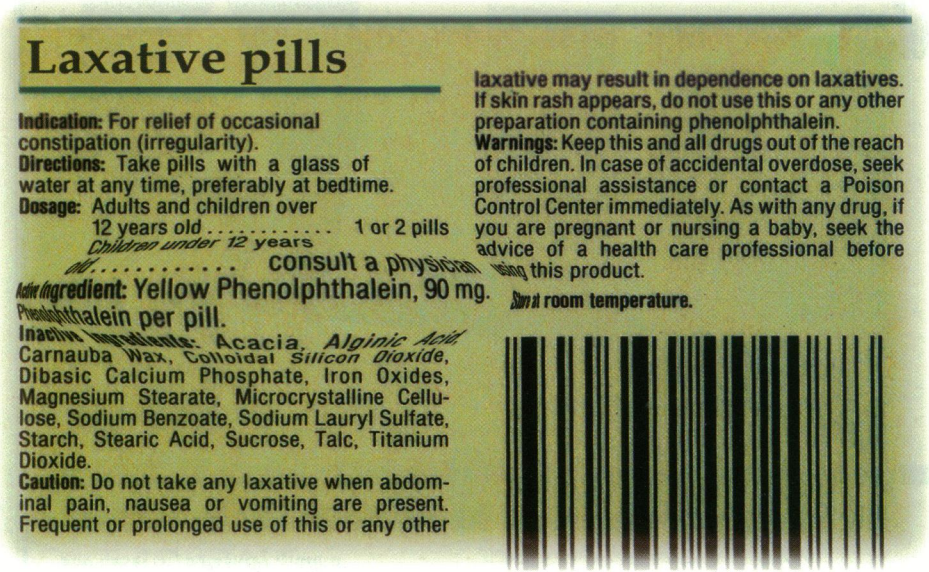
In December scientists announced that phenolphthalein, a substance used for almost a century in over-the-counter laxatives, showed clear evidence of carcinogenicity in rodent studies and may present a risk to humans, particularly individuals who ingest amounts greatly exceeding recommended doses.

The determination was made by the National Toxicology Program, which initiated toxicology and carcinogenicity studies of phenolphthalein because no long-term animal studies were available to allow evaluation of the potential risks to humans from prolonged use of the drug. The National Cancer Institute had nominated phenolphthalein for study.

In the NTP studies, rats and mice were fed phenolphthalein over a period of two years at doses of 12,000, 25,000, and 50,000 parts per million (ppm) to rats and 3,000, 6,000, and 12,000 ppm to mice. The rodents were then examined for the presence of cancerous and noncancerous pathology. The study results are summarized as follows:

- clear evidence of carcinogenic activity in male F344/N rats based on markedly increased incidences of benign neoplasms of the adrenal medulla and benign and malignant neoplasms of the kidneys;
- some evidence of carcinogenic activity in female rats based on increased incidences of benign pheochromocytoma in the 12,000 ppm dose group, and of benign or malignant neoplasms of the adrenal medulla;
- clear evidence of carcinogenic activity in male mice based on histiocytic sarcoma and malignant lymphoma;
- clear evidence of carcinogenic activity in female mice based on increased incidences of histiocytic sarcoma, malignant lymphoma of all types, lymphoma of thymic origin, and benign ovarian tumors.

According to the NTP, phenolphthalein may cause cellular alterations in animals by a number of mechanisms including chromosomal damage, and through estrogenlike activity. Additional studies are underway to further understand the mechanisms by which phenolphthalein acts. The NTP technical report on phenolphthalein stresses, however, that it is difficult to extrapolate human risk from animal studies, and no population studies of phenolphthalein users have shown an increased risk for disease. This does not mean, however, that the drug is necessarily risk-free for humans. George Lucier, director of the Environmental Toxicology Program at the NIEHS, says, "Although we can't precisely determine the relevance of the NTP animal findings for human risk, they do provide a red flag of caution."



Unwanted ingredient? New research shows phenolphthalein, a drug found in many laxatives, may have carcinogenic side effects in animals.

Alternatives in Animal Testing

The three "R's" of animal testing are refine, reduce, and replace. Respectively, they denote modifying toxicological test procedures to lessen or eliminate animals' pain, curtailing the number of animals required for a test, and substituting test animals with non-animal methods or phylogenetically lower species. Total replacement would mean eliminating the use of animals by using microbes, cells, tissues, and other *in vitro* methods, as well as using computerized information databases and mathematical models.

Applying the three Rs to the development and validation of new and improved testing methods is mandated by Section 1301 of the National Institutes of Health Revitalization Act of 1993 (PL 103-43). The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was established at the NIEHS in 1994 to fulfill this mandate by establishing criteria for the validation of alternative testing methods, and recommending processes by which they can be accepted for regulatory use.

This daunting task was discussed at the National Toxicology Program Workshop on Validation and Regulatory Acceptance of Alternative Toxicological Test Methods, held in Arlington, Virginia, 11–12 December 1995. The workshop was organized by ICCVAM, which consists of *ad hoc* representatives of 15 federal scientific and regulatory agencies. The purpose of the public workshop was to obtain comments and recommendations from experts and interested stakeholders from industry, academia, government, public interest groups, and animal welfare organizations on a draft report prepared by the committee. The draft report and workshop report was presented at an Organization for Economic Cooperation and Development (OECD) workshop on toxicological test alternatives held in January 1996 in Stockholm, Sweden. Neil Wilcox, special assistant to the associate commissioner of the FDA, said, "The forum successfully brought key individuals togeth-